NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2004

PLAN FOR HIV-RELATED RESEARCH

I: OVERVIEW

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

Foreword

As the Director of the Office of AIDS Research (OAR), I am pleased to present the National Institutes of Health (NIH) Fiscal Year 2004 Plan for HIV-Related Research. Each year, we develop a comprehensive research plan through a unique collaborative process involving broad input from the community of government and nongovernment scientists and other experts from the United States and abroad. It is essential that the Plan be responsive to the changing nature of the epidemic, to emerging scientific opportunities, and to the needs of affected communities around the world. The input of these experts helps to ensure such responsiveness.

Many individuals—researchers from academia and industry; representatives of foundations and other nongovernmental organizations in the United States and abroad; community representatives; representatives of other governmental agencies; members of the OAR Advisory Council; and Directors of the NIH Institutes and their staffs—have given generously of their time to provide us with their expertise and thoughtful opinions in the development of this Plan. I thank each of them, for it is their thoughtful consideration and advice that makes this document a valuable tool for the OAR and NIH.

Through this planning effort, we attempt to articulate a roadmap for the NIH research effort that both comprehensively defines the full range of activities needed to combat HIV and AIDS and identifies specific priorities for new or expanded funding. The Plan serves as the framework for the development and execution of the NIH AIDS budget and thus is an integral

component of the budgeting process, providing essential guidance for funding decisions.

The staff of the OAR and I sincerely believe that the fruits of the research efforts outlined within the Plan will help to control the pandemic, prevent new infections, and care for those infected and affected by HIV and AIDS around the world.

Jack Whitescarver, Ph.D.
Director, OAR
May 2002

Legislative Mandate

The National Institutes of Health Revitalization Act of 1993 (Public Law 103-43) provided that the Director of the Office of AIDS Research (OAR) "shall plan, coordinate and evaluate research and other activities conducted or supported" by NIH. The Director of OAR "shall act as the primary Federal official with responsibility for overseeing all AIDS research conducted or supported by the National Institutes of Health" and "shall establish a comprehensive plan for the conduct and support of all AIDS activities of the agencies of the National Institutes of Health...; ensure that the Plan establishes priorities among the AIDS activities that such agencies are authorized to carry out; ensure that the Plan establishes objectives regarding such activities...; and ensure that the Plan serves as a broad, binding statement of policies regarding AIDS activities of the agencies, but does not remove the responsibility of the heads of the agencies for the approval of specific programs or projects, or for other details of the daily administration of such activities, in accordance with the Plan." The law further provides that "the Director of the OAR shall ensure that the Plan provides for basic research; provides for applied research; provides for research that is supported and conducted by the agencies; provides for proposals developed pursuant to solicitations by the agencies and for proposals developed independently of such solicitations; and provides for behavioral research and social science research."

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Introduction

THE GLOBAL HIV/AIDS PANDEMIC

AIDS is the greatest international health challenge of our time. HIV has already infected more than 60 million people around the world, and AIDS has killed approximately 25 million people, surpassing tuberculosis (TB) and malaria as the leading infectious cause of death worldwide. If the global spread of HIV/AIDS continues unchecked, South and Southeast Asia and perhaps China will follow the disastrous course of sub-Saharan Africa. Rapid increases in HIV infection also are occurring in Eastern Europe and Central Asia, and AIDS represents a serious threat in Latin America and the Caribbean.

Group	People Newly Infected in 2001	People Living with HIV/AIDS	AIDS Deaths in 2001	Total AIDS Deaths
Adults	4.3 Million	37.2 Million	2.4 Million	19.9 Million
Women	*1.8 Million*	*17.6 Million*	*1.1 Million*	*10.1 Million*
Children	800,000	2.7 Million	580,000	4.9 Million
Total	**5.0 Million**	**40.0 Million**	**3.0 Million**	**24.8 Million**

Source: UNAIDS

Recent data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) indicate that worldwide there are now almost equal numbers of men and women infected with HIV. In sub-Saharan Africa, the UNAIDS/World Health Organization (WHO) estimated that 28.1 million adults and children were living with HIV/AIDS at the end of 2001. Women represented 55 percent of the adults living with HIV disease. Curbing the transmission of HIV from infected mother to infant is an especially compelling challenge in resource-poor countries.

The coexistence of other endemic diseases widely prevalent in diverse geographic areas, such as respiratory and gastrointestinal infections, complicate care and treatment and pose additional problems for medical personnel caring for HIV-infected individuals. Of particular note is the parallel epidemic of TB in the developing world. Attitudes, beliefs, and taboos surrounding sex, the status of women and children, and the source and etiology of HIV can complicate attempts to control transmission and provide appropriate prevention and treatment.

THE EPIDEMIC IN THE UNITED STATES

The Centers for Disease Control and Prevention (CDC) estimates that just under a million people are living with HIV infection in the United States, one quarter of whom are unaware of their infection. Through June 2001, the cumulative number of AIDS cases reported to the CDC in the United States totaled 793,026.

The HIV/AIDS epidemic in the United States continues to evolve. The incidence of new AIDS cases has declined, due largely to expanded use of new antiretroviral therapies that slow the progression of HIV infection to AIDS. However, the decline in death rates observed in the late 1990s has now leveled off and, more disturbingly, the rate of new HIV infections has not changed since 1990 and remains constant at about 40,000 new infections each year, according to CDC estimates. This means that the overall epidemic is continuing to expand. In fact, HIV infection rates are continuing to climb among women, racial and ethnic minorities, young homosexual men, individuals with addictive disorders, and people over 50 years of age.

According to CDC reports, approximately one quarter of the HIV-infected population in the United States also is infected with hepatitis C virus (HCV). HIV/HCV co-infection is found in 50 to 90 percent of injecting drug users (IDUs). HCV progresses more rapidly to liver damage in HIV-infected persons and may also impact the course and management of HIV infection, as HIV may change the natural history and treatment of HCV.

AIDS disproportionately affects African Americans and Hispanics. According to CDC figures through June 2001, among infected women in the United States, approximately 64 percent are African American and 18 percent are Hispanic. Among newly infected men, approximately 50 percent are African American and 20 percent are Hispanic.

The continued expansion of the epidemic as well as the increasing incidence of multidrug-resistant strains of HIV forebode an epidemic of even greater magnitude in the coming years.

THE NIH AIDS RESEARCH PROGRAM

To respond to this pandemic, NIH has developed a comprehensive biomedical and behavioral research program to better understand the basic biology of HIV, develop effective therapies to treat and control HIV disease, and design interventions to prevent new infections from occurring. NIH supports AIDS research both in NIH intramural laboratories and at academic and medical institutions in the United States and internationally. The Office of AIDS Research (OAR) is mandated by public law to plan and coordinate the AIDS research programs sponsored by all of the NIH Institutes and Centers (ICs).

The Role of the Institutes

Nearly every NIH component supports HIV/AIDS-related research activities, consistent with its individual mission. A list of NIH ICs is found in Appendix A of this Plan. The ICs whose research programs are most heavily focused on HIV, AIDS, and their sequelae are the National Institute of Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), the National Center for Research Resources (NCRR), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Child Health and Human Development (NICHD). The Warren Grant Magnuson Clinical Center provides the infrastructure for intramural clinical studies sponsored by the ICs. A summary of HIV/AIDS funding by IC for fiscal years 2001–2003 is provided in Appendix B.

Office of AIDS Research

Mission: OAR, located within the Office of the Director (OD), was established in 1988 to coordinate the scientific, budgetary, legislative, and policy elements of the NIH AIDS research program and to serve as the principal liaison with the Department of Health and Human Services (DHHS), other Federal agencies, and domestic and international governmental and nongovernmental organizations on behalf of NIH AIDS-related research. NIH represents the largest and most significant public

investment in AIDS research in the world. Our response to the epidemic requires a unique and complex multi-Institute, multidisciplinary, global research program. Perhaps no other disease so thoroughly transcends every area of clinical medicine and basic scientific investigation, crossing the boundaries of the NIH ICs. This diverse research portfolio demands an unprecedented level of scientific coordination and management of research funds to identify the highest priority areas of scientific opportunity, enhance collaboration, minimize duplication, and ensure that precious research dollars are invested effectively and efficiently. This is recognized in the unique role given OAR, relative to other OD offices, in its authorizing legislation, the NIH Revitalization Act of 1993. That law establishes OAR as a model for trans-NIH coordination, vesting it with primary responsibility for overseeing all NIH AIDS-related research, and thus allowing NIH to pursue a united research front against the global AIDS epidemic.

Evaluation: OAR has authority to evaluate NIH AIDS-related research programs. Several years ago, OAR completed a major evaluation of the entire NIH AIDS research program, utilizing the expertise of nongovernment scientists and AIDS community representatives. That review led to a number of significant changes in the overall direction of the AIDS research program, including bringing new focus to such areas as human immunology, vaccine research, and other areas of HIV prevention science. OAR continues to support periodic reviews of areas of AIDS research as well as specific programs across the Institutes.

Trans-NIH Coordination: OAR plays a crucial role in identifying scientific areas that require focused attention and facilitating multi-Institute activities to address those needs. This is a two-way process. In some cases these issues are raised within OAR and shared with the Institutes; in other cases, one or more Institute may ask OAR to bring other Institutes together to address an area of research or to co-sponsor a specific grant, project, or initiative. OAR can foster these efforts through a number of mechanisms, such as establishing working groups or committees; sponsoring workshops or conferences to highlight a particular research topic; sponsoring reviews or evaluations of research program areas to identify scientific opportunities, gaps, or needs; and designating funds and supplements to jump-start program areas.

For example, a number of years ago OAR identified microbicides research as an area needing additional attention. Microbicides research has proved particularly challenging, as there is no definitive clinical evidence as yet establishing that a product applied topically in humans can prevent HIV transmission. To enhance and facilitate research in this area, OAR established

a Trans-NIH Microbicides Working Group, comprised of program staff of relevant Institutes and offices; co-sponsored the first international conference on microbicides; spearheaded the development of an NIH Strategic Plan for Microbicides and a broader government-wide plan; and provided supplemental funds to the Institutes to accelerate microbicide research.

OAR also has placed high priority on research to address the disproportionate impact of the epidemic on racial and ethnic minority communities in the United States. OAR is directing increased resources toward (1) new and innovative interventions that will have the greatest impact on these groups and (2) efforts to improve research infrastructure and training opportunities for minorities.

International AIDS Research: Another area of OAR leadership is in addressing the urgency of the global AIDS epidemic. OAR coordinates, monitors, and fosters plans for NIH involvement in international AIDS research and training activities. OAR has established a new initiative and strategic plan for global research on HIV/AIDS aimed at slowing the pandemic and reversing its devastating effects on individuals, communities, economies, and nations worldwide. The Global AIDS Research Initiative and Strategic Plan and the budget commitment that derives from it reaffirm NIH's long-standing support for international AIDS research and will help to significantly expand our efforts to benefit resource- and infrastructure-poor nations.

Organization: An "AIDS Coordinator" is designated in each IC who serves as the point of contact with OAR. OAR is required by law to establish and support Coordinating Committees for each research discipline of AIDS research. These committees allow OAR to stay abreast of the scientific programs across NIH, to foster collaboration and coordination, and to develop the annual NIH plan and budget. OAR senior staff chair these coordinating groups and work with the Institutes to facilitate research. The OAR Advisory Council provides expert advice to the Director of OAR and DHHS Secretary. Its members include nongovernment experts from a broad array of scientific disciplines as well as AIDS community representatives; representatives of Advisory Councils from the NIH Institutes with the largest AIDS research portfolios; and representatives from other Federal agencies conducting AIDS research, including the Department of Defense, the Department of Veterans Affairs, and the CDC, providing further opportunity for coordination and collaboration.

Priority-Setting Through Planning: Each year, OAR oversees the congressionally mandated development of the comprehensive NIH AIDS-related research plan and budget, based on scientific consensus about the

most compelling scientific priorities and opportunities that will lead to better therapies and prevention strategies for HIV disease. The planning process is inclusive and collaborative, involving the NIH Institutes through a series of trans-NIH Coordinating Committees, as well as eminent nongovernment experts from academia, foundations, and industry, with the full participation of AIDS community representatives.

Historically, the Plan has established the NIH AIDS research agenda in the following Scientific Areas of Emphasis: Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; and Behavioral and Social Science. As the epidemic evolved, OAR recognized the need to bring additional focus to a number of cross-cutting areas. Thus, the Plan now also addresses the areas of Racial and Ethnic Minorities; Women and Girls; Microbicides; HIV Prevention Research; International Research; Training, Infrastructure, and Capacity Building; and Information Dissemination.

Trans-NIH Comprehensive AIDS Research Budget: The law provides that OAR shall allocate all appropriated AIDS research funds to the Institutes. The Plan initiates the annual budget development and allocation process. Based on the priorities and objectives established in the Plan, the ICs submit their AIDS-related research budget requests to OAR, focusing on new or expanded program initiatives for each scientific area. OAR reviews the IC initiatives in relation to the Plan, to OAR priorities, and to other IC submissions to eliminate redundancy and/or to assure cross-Institute collaboration. The NIH Director and the OAR Director together determine the total amount allocated for AIDS research within the overall NIH budget, as required by law. Within that total, OAR allocates the AIDS research budget levels to each IC, based on the scientific priority of the proposed initiatives, at each step of the budget development process up to the time of the final congressional appropriation. This involves consulting regularly with the IC Directors and maintaining knowledge of the ongoing scientific research programs and planned initiatives supported by each IC. This process allows OAR to ensure that NIH AIDS-related research funds will be provided to the most compelling scientific opportunities, rather than distributed simply by a formula.

As congressionally mandated, OAR also prepares an annual "by-pass" budget for submission directly to the President. This by-pass is essentially a professional judgment budget, based solely on scientific need and opportunity, without regard to cost.

OVERVIEW OF THE PLAN

The Planning Process

OAR has established a unique and effective model for developing a consensus on scientific priorities for the annual comprehensive *NIH Plan for HIV-Related Research*. To develop the FY 2004 Plan, OAR sponsored a series of planning workshops to seek the input of non-NIH experts from academia, foundations, industry, and the community. These experts participated with NIH scientific and program staff in Planning Groups for Natural History and Epidemiology; Etiology and Pathogenesis; Therapeutics; Vaccines; Behavioral and Social Science; Microbicides; HIV Prevention Research; Racial and Ethnic Minorities; Women and Girls; and International Research. A list of participants in the Planning Groups is found in their respective sections of the FY 2004 Plan. Participants in each Planning Group were asked to review and revise the objectives and strategies of the Plan, based on the state of the science, and to identify a set of priorities for their area. All groups were asked to address needs in Information Dissemination and Training, Infrastructure, and Capacity Building as related to their area. The resulting draft Plan was then provided to each IC Director and AIDS Coordinator for recommendations and comments. Finally, the Plan was reviewed by the Office of AIDS Research Advisory Council (OARAC). A list of current OARAC members is included in Appendix C. OAR continues to reassess the planning process and make refinements in order to better capture the broadest range of scientific expertise and community participation and to facilitate the identification of specific scientific priorities.

Structure of the Plan

The structure of the Plan is designed to (1) comprehensively describe research activities that are needed to address HIV and AIDS; (2) define specific research priorities; and (3) reflect mutual reinforcement among the scientific and cross-cutting areas. Each of these sections of the Plan includes (1) Scientific Issues and Priorities and (2) Objectives and Strategies.

Scientific Issues and Priorities: This section provides a scientific overview and specific priorities identified by the planning groups. These priorities narrowly define a few key areas deemed most worthy of new or expanded funding based on the current scientific knowledge, opportunities, and gaps. They will be used to guide the development of the FY 2004 AIDS budget and to adjust the FY 2003 AIDS budget as needed.

Objectives and Strategies: This section consists of a comprehensive list of Objectives, in priority order, that address the many needs and challenges within the field of HIV/AIDS research. Each Objective is followed by a set

of Strategies that provide examples of approaches that might be taken to fulfill each Objective. To underscore the interrelationships among areas, strategies may be found under more than one Area of Emphasis.

Uses of the Plan

The Plan serves several important purposes:

- As the framework for developing the NIH AIDS research budget. A chart showing the relationship between the planning and budget process may be found in Appendix D.
- For determining the use of NIH AIDS-designated dollars and for tracking and monitoring those expenditures. The Plan thus defines those research areas for which AIDS-designated funds may be allocated.
- As a document that provides information to the public, the scientific community, Congress, and the AIDS-affected communities about the NIH AIDS research agenda. OAR distributes the annual comprehensive Plan to a wide audience, and it appears on the OAR Web site: http://www.nih.gov/od/oar.

Major Themes of the Plan

The FY 2004 NIH AIDS research agenda continues the following overarching themes: HIV prevention research, including development of vaccines, microbicides, behavioral interventions, and strategies to prevent perinatal transmission; therapeutics research to develop simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated illnesses, malignancies, and other complications; international research, particularly to address the critical research and training needs in developing countries; and research targeting the disproportionate impact of the AIDS epidemic on racial and ethnic minority populations in the United States. All of these efforts require a strong foundation of basic science. The key priorities for each research area of the Plan and directions for future research are summarized below.

NATURAL HISTORY AND EPIDEMIOLOGY

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Structure epidemiological studies in domestic and international communities to characterize risk factors for transmission and assess the impact of interventions (antiviral therapy, prevention programs, etc.) on HIV incidence, risk behaviors, and outcomes of infection in adult and pediatric populations.**
- **Develop and implement studies to provide epidemiologic data that will serve as the basis for intervention trials in domestic and international locales.**
- **Develop and evaluate accurate, reproducible, and affordable virologic, immunologic, pharmacologic, and genetic assays; measures of adherence to therapy; and markers of recent infection for large-scale use in domestic and international settings.**
- **Develop, maintain, and effectively utilize domestic and international cohorts, repositories, and nested studies among populations experiencing emerging and ongoing HIV epidemics. Use this approach to increase the understanding of natural history, treated history, and pathogenesis of HIV infection and disease, including adverse events in the presence of interventions.**
- **Enhance our understanding of the interactions between the epidemiology, prevention, treatment, and management of HIV and concomitant infections and disorders. Investigate the implications of concomitant infections on immunogenicity and efficacy of HIV vaccine candidates.**

Natural history and epidemiologic research is needed to monitor epidemic trends, develop and evaluate prevention modalities, follow the changing clinical manifestations of HIV disease in different populations, and measure the effects of treatment regimens. NIH will continue to support research to examine topics in HIV transmission, HIV/AIDS disease progression (including the occurrence of co-infections), malignancies, metabolic complications, neurological and behavioral dysfunctions, and the development of other HIV/AIDS-related conditions. Domestically as well as internationally, the populations affected by HIV/AIDS are also those most severely affected by the spreading epidemics of sexually transmitted diseases (STDs), hepatitis C, and TB. Further studies are needed to investigate the effects of viral, host, and other factors on transmission and disease progression. Results from these studies will provide new directions and improvements in HIV/AIDS prevention and care.

The effects of the new antiretroviral therapies on HIV transmission are not completely understood. A few studies suggest that individuals on antiretroviral therapy may be less likely to transmit HIV infection because they have lower viral loads after treatment. The result of this phenomenon may be a decrease in the rates of transmission and HIV incidence. However, the net effect of the perception that individuals on antiretrovirals may be less likely to transmit HIV infection may be that more people are taking increased sexual risks. Thus, the paradoxical consequence of the lower viral loads that result from antiretroviral therapies may be higher rates of HIV transmission and infection. Because biological, pharmacological, psychological, and behavioral factors all potentially influence the impact of antiretroviral therapies on HIV transmission, there is a need to evaluate the specific contributions of these factors and their net impact on HIV transmission.

Another area of primary prevention research focuses on developing new or improved means of reducing transmission of HIV from an infected mother to her child in the United States and worldwide, with particular emphasis on methods appropriate to the developing world. NIH is supporting studies to better understand the timing, mechanisms, and risk factors of this transmission; whether specific strains are more likely transmitted; the potential benefit of Caesarean section; and development of newer and better therapeutic regimens and immunotherapy. The elimination of mother-to-child transmission (MTCT) in our Nation and the world is a goal that is being vigorously pursued.

NIH will continue to emphasize the importance of epidemiologic cohort studies to investigate the mechanisms of disease progression, the causes of death, and the impact of therapy in changing the spectrum of HIV disease. The strengthening of existing cohorts in the United States will allow the identification of long-term effects of HIV therapy. The assembly of new, representative cohorts, specimen repositories, and databases in developing countries will be important to study key co-factors (e.g., infectious and nutritional) that modify HIV disease.

Like many other diseases in the United States, HIV/AIDS has become concentrated in urban, disenfranchised communities of low socioeconomic status, as well as in certain racial and ethnic minority groups (i.e., African Americans and Hispanics). A determination of the biological characteristics, sociocultural factors, and health services issues that contribute to the differential dynamics of HIV transmission and disease progression in men, women, and in different race/ethnicity groups is needed for developing appropriate prevention and treatment strategies across at-risk populations in domestic and international settings.

The availability of accurate and reproducible laboratory assays has become one of the most important means to rapidly acquire knowledge of the HIV epidemic in different populations and geographic areas. Molecular biology methods are invaluable to determine key viral and host features that can be used for screening, diagnosis, and prognosis. In developing countries, simple and affordable assays are necessary to define the epidemiologic features of emerging or evolving epidemics and for clinical use in hard-to-reach locales. NIH will foster basic and applied research that will develop inexpensive virologic, immunologic, and genetic assays for use in both domestic and developing country settings.

ETIOLOGY AND PATHOGENESIS

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Facilitate the translation of new insights into HIV biology to develop novel interventions for the prevention and treatment of HIV infection.**
- **Elucidate the biologic determinants of HIV transmission between individuals and define the mechanisms by which host factors, viral factors, and co-factors may influence the process of virus transmission.**
- **Characterize the dynamic of virus-host interaction through the course of HIV infection.**
- **Investigate the mechanisms of persistence of HIV infection.**
- **Define the direct and indirect mechanisms that lead to T-cell depletion following HIV infection and the factors that determine numerical and functional reconstitution of T-cell populations in response to therapy.**
- **Enhance and expand innovative studies of human immunology to guide vaccine development and immune reconstitution efforts.**
- **Investigate the impact of gender, health status, race, and age on the biology of HIV infection and on the responses to therapies and vaccines.**
- **Advance the understanding of the mechanisms responsible for the toxicities and long-term complications of antiretroviral therapy (ART) and the factors that underlie changes in the causes of morbidity and mortality in an era of increasingly effective therapies.**

Of paramount importance in our fight against HIV/AIDS is maintaining a strong commitment to basic research. Tremendous progress has been made in understanding the fundamental steps in the life cycle of HIV, the host-virus relationship, and the clinical manifestations associated with HIV infection and AIDS. Groundbreaking research on basic HIV biology and AIDS pathogenesis has revolutionized the design of drugs, the methodologies for diagnosis, and monitoring for efficacy of antiviral therapies. In spite of these achievements, we still do not have a clear understanding of major aspects of the interaction of HIV with the infected individual, the nature of the immune response to the virus, how the virus establishes infection and spreads throughout the body, and its mechanisms of pathogenesis. This basic knowledge is critical for our efforts to prevent

and control HIV infection and disease progression. A substantial portion of NIH AIDS-related research will continue to be devoted to basic research. This area of investigation, driven by investigator-initiated research, has provided the constantly advancing knowledge base that permits the development of new applications for the prevention and treatment of disease.

Some of the outstanding questions within the area of etiology and pathogenesis research include: What role do the specific products of HIV (the viral genes and their protein products) play in the viral life cycle in individual cells and within the body of infected individuals? How is HIV transmitted between cells and between individuals? What contribution does the immune system make to controlling the infection and to the disease process? What mechanisms are involved in cell injury and death in the immune, nervous, and other systems that HIV afflicts? What host factors and co-factors influence the course and outcome of HIV infection? What is the relationship of HIV infection to the associated malignancies, co-infections, neurological impairments, and metabolic disturbances that characterize AIDS?

The dramatic success of effective ARTs in reducing plasma viremia to undetectable levels had raised the intriguing possibility that prolonged therapy might lead to virus eradication. However, recent data have indicated that the virus can persist in the body of HIV-infected patients for almost a lifetime. HIV can persist in a latent reservoir of resting memory CD4 T cells that is established very early after infection and by continuously replicating, albeit at very low levels, even in the presence of ARTs able to drive viral load below the limits of detection. A better understanding of the different mechanisms of viral persistence is needed to understand the reasons for drug failure, to design rational approaches for virus eradication, and to better assess the impact of persistence on HIV transmission and its implications for HIV prevention.

Understanding the normal development and functioning of the human immune system is crucial to our ability to understand the effects of HIV on the immune system and the pathogenesis of AIDS. This understanding also holds the key to designing rational immune reconstitution approaches in persons undergoing antiretroviral treatment and identifying the characteristics of the immune response that are needed for a protective vaccine.

The basic science underlying HIV etiology and pathogenesis research is generally gender neutral. Basic mechanisms of viral replication and pathogenesis are not expected to differ in women and men. However, there are differences in the way HIV infection is transmitted and how the disease

is manifested in women and men. Studies have been designed to elucidate the pathogenic mechanisms more commonly observed in women, children, and adolescents infected with HIV. Transmission of HIV from a mother to her infant may occur *in utero* through transplacental passage of virus, during delivery, or postnatally through breast-feeding. Many basic issues associated with maternal-fetal transmission remain unclear and are actively under investigation.

To ensure the continued growth of a powerful arsenal against HIV, it is imperative that scientists continue to study HIV pathogenesis and identify new targets for the design of drugs and vaccines. Design and development of new drugs are based on the study of the fundamental structural properties of the relevant viral targets. Efforts to develop effective therapies to treat HIV infection and its associated illnesses are providing a critical proving ground for the concept of rational drug design and for the refinement and advancement of its methods.

AIDS is associated with a broad spectrum of cancers and tumors. Because HIV causes immunosuppression and most AIDS-associated malignancies are strongly associated with viruses, HIV infection provides a unique model to study the interplay of viruses, a dysfunctional immune system, and the development of cancers. Elucidation of the interactive factors involved in the pathogenesis of AIDS-associated malignancies will possibly translate into the identification of new targets for prevention and treatment.

HIV infection results in progressive damage of the immune systems of infected individuals and makes them susceptible to a diverse collection of bacteria, viruses, fungi, and protozoa that represent the major causes of suffering and death for HIV-infected individuals. Of particular note is the emerging incidence of co-infection with HCV. Co-infections can affect virtually every tissue and organ system in the body, resulting in severe functional compromise. NIH currently supports a comprehensive portfolio of basic research on the pathogenesis of AIDS-associated co-infections.

THERAPEUTICS

RESEARCH PRIORITIES OF THE FY 2004 PLAN

Preclinical Development of New Therapeutic Agents

- **Advance the discovery and validation of new viral and cellular targets.**
- **Develop new therapeutic agents that: target drug-resistant virus; have activity in viral reservoirs and cellular compartments; and have improved pharmacologic properties.**
- **Develop *ex vivo* and/or animal models to evaluate the biological properties of drugs, including their pharmacology and toxicology.**

Mother-to-Child Transmission Intervention

- **Develop therapeutic regimens to block MTCT that can be implemented in developed and developing nations. Develop safe, effective, feasible, and conveniently administered strategies to interrupt MTCT of HIV. Focus on international studies to inhibit MTCT of HIV with special emphasis on breast-feeding.**
- **Evaluate the safety and pharmacokinetics of antiretroviral agents in pregnant and breast-feeding women, including studies on the transplacental passage of the agents and safety for the fetus.**
- **Evaluate pharmacokinetics, metabolism, tissue absorption, and drug elimination in the newborn.**
- **Conduct studies to evaluate and reduce short- and long-term toxicity of antiretroviral drugs in women during pregnancy, and their offspring who were perinatally exposed.**

Development of Immunology Therapeutics

- **Develop and evaluate therapeutic approaches that will improve and sustain immune function or prevent transmission of HIV infection.**
- **Identify and validate markers to predict the efficacy of immune-based therapies.**

Clinical Evaluation of Therapies

- **Determine optimal therapeutic strategies including when to start (early versus late), change, sequence, or interrupt therapies and evaluate therapeutic drug monitoring strategies.**

- **Identify regimens with improved toxicity, efficacy, pharmacokinetics, activity in viral reservoirs, adherence potential, and reduced cost.**
- **Target populations, especially women, IDUs, children, adolescents, older adults, and across racial/ethnic groups. Conduct studies that permit evaluation of potential differences in response to therapy due to gender and/or racial/ethnic differences.**
- **Enhance capabilities for long-term followup and evaluate the long-term effects of therapy, including delayed or late toxic effects.**
- **Conduct studies to determine the most medically advantageous time to initiate therapy and the implications of these findings on public health.**
- **Perform studies to evaluate the impact of treatment regimens to prevent HIV transmission.**
- **Identify treatment regimens that promote adherence and compliance.**

Evaluation of Co-Infection

- **Evaluate the effects of co-infection especially with hepatitis B virus (HBV), HCV, or TB, on the management of HIV. Determine the bidirectional effects of co-infection and treatments on disease progression and drug interactions.**
- **Develop new agents for the treatment of HBV, HCV, and TB in the setting of HIV infection, with specific attention to pharmacologic drug interactions and nonoverlapping toxicity.**

International

- **Expand international clinical research programs in countries with limited resources.**
- **Design and conduct clinical studies that are appropriate for diverse international settings.**
- **Design studies to improve and facilitate the delivery of therapeutic interventions for HIV disease.**
- **Evaluate the clinical and public health impact of antiretroviral treatment.**
- **Evaluate the clinical and public health impact of prophylactic and therapeutic interventions for co-infections/opportunistic infections (OIs).**

- **Encourage studies that integrate therapeutic regimens and prevention interventions.**

The development of therapeutics for HIV infection and AIDS has long been a focus of NIH. Today, many HIV-infected people are living with the benefits resulting from NIH-supported research in this area. The development of combination regimens including protease inhibitors has extended the length and quality of life for many HIV-infected individuals in the United States and Western Europe. Unfortunately, however, ART has failed to eradicate HIV, and a growing proportion of patients receiving therapy experience treatment failure. Some patients find it difficult or impossible to comply with arduous treatment regimens, develop toxicities and side-effects, or cannot afford their high cost of approximately $15,000 per year. Others fail to obtain a satisfactory reduction in viral load even while adhering to treatment regimens. In addition, metabolic complications, including insulin resistance, and body composition changes such as deforming deposits of abdominal adipose tissue have emerged in individuals who have been on long-term antiretroviral regimens. Finally, an increasing number of treatment failures are linked to the emergence of drug-resistant HIV.

The need for simpler, less toxic, and cheaper drugs and drug regimens to treat HIV infection and its associated co-infections; malignancies; and other complications, such as HCV infection, continues to be a high priority. This includes the discovery and development of the next generations of antiviral drugs directed against new cellular and viral targets. Clinical trials will help to better define when to begin and/or switch drugs within a regimen as well as to identify regimens for treatment-experienced individuals who no longer respond to these anti-HIV drugs. Antiretroviral and OI prophylaxis regimens are becoming increasingly complex with respect to drug-drug interactions and adherence. Protease inhibitors, in particular, interact with each other and many other medications commonly used by HIV-infected individuals. Additional research is under way and planned with the goal of minimizing viral replication and delaying disease progression, drug resistance, and development of manifestations such as metabolic complications and body composition changes. Further studies also are needed to evaluate delayed and long-term effects of these antiretroviral drugs.

The scientific agenda for this area of research is answering the following questions: When should ARTs be initiated? When should they be changed? How long can successful therapies maintain decreased viral loads, increased CD4 counts, and improved clinical outcomes? What is the basis for the emergence of drug resistance, and how can it be prevented? What are the

long-term clinical efficacy and tolerability associated with ART? Can treatment strategies be developed for patients who no longer respond to current regimens? Can immune-restorative/immune-enhancing approaches rebuild the immune system so that disease progression is delayed? Can treatment strategies be developed to eliminate HIV so that it is not transmitted from an infected individual to others?

Recent advances in therapeutics research underscore the importance of continued and further collaboration of government- and industry-sponsored drug development research and clinical trials with the common goal of developing therapeutic regimens that slow disease progression, extend life spans, and improve the quality of life for HIV-infected individuals.

VACCINES

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Continue to pursue multiple approaches to develop expanded access to nonhuman primates (NHP) for studies of HIV/AIDS vaccines, with emphasis on models that employ alternatives to rhesus macaques of Indian origin; support collaborative studies and reagent development in additional species to avoid duplicative experiments.**
- **Ensure minimal lag time between testing of novel approaches to induce broadly cross-reactive antibodies against HIV-1 envelope in small animals and testing in human clinical trials by working with investigators who are developing these approaches and advancing promising candidates rapidly into comparative testing; outsource central resources, develop new facilities to produce GMP products, and/or foster academic-private sector partnerships as needed.**
- **Systematically examine the clade specificity issue for HIV vaccines in clinical studies in multiple sites both in the United States and in international sites through studies to evaluate cross-clade immune response; develop standardized assays, quality assurance, and quality control of reagent panels for preclinical and clinical studies; and establish infrastructure to enroll and study populations.**
- **Support studies to identify populations of young people where the risk of HIV transmission is high and engage them in culturally sensitive education efforts about vaccines and vaccine trials; address ethical and legal concerns related to this vulnerable population.**
- **Invest now in training activities that will develop trained investigators with links to the communities in which HIV vaccines will be tested, including populations in developing countries as well as some underserved populations in the United States.**

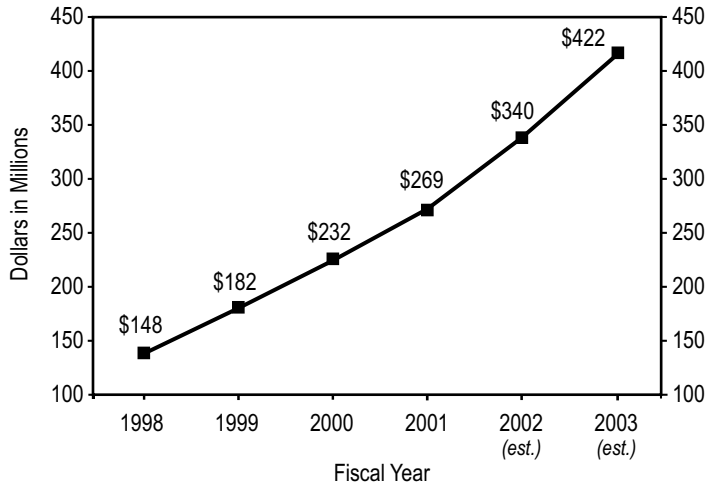
A safe and effective HIV preventive vaccine is essential for global control of the AIDS pandemic. NIH funding for HIV vaccine research increased by more than 185 percent between FY 1998 and FY 2003, resulting in the award of new grants to foster innovative research on HIV vaccines, including vaccine design and development and the invigoration and reorganization of the NIH vaccine clinical trials effort. The new intramural Dale and Betty Bumpers Vaccine Research Center recently initiated its first clinical trial. In February 1999, NIH-supported investigators initiated the first AIDS vaccine

trial in Africa. The changes implemented in this area over the past few years have enormous significance, not only for AIDS research but for other diseases as well, as progress made in the development of an AIDS vaccine will have implications for vaccines against other life-threatening illnesses.

Recent progress in HIV/AIDS vaccine research using animal models has provided strong scientific motivation to further explore and develop several vaccine concepts, and to move additional candidate vaccines into clinical testing. As a result of increased funding from NIH in the area of HIV vaccines, many new approaches to HIV vaccines are being pursued from basic research in vaccine design and studies of immune responses in small animals through vaccine product development. At least 10 new candidate vaccines will enter Phase I clinical trials in the next 2 years.

To address the scientific obstacles and facilitate AIDS vaccine development, NIH continues to increase support for a broad program encompassing basic, preclinical, and clinical vaccine research on candidate vaccine products. As promising vaccines move further in the vaccine pipeline, expanded trials with populations at increased risk for HIV infection will become increasingly important. HIV/AIDS vaccine research requires trained health care, medical research, and prevention specialists as well as populations at risk who will be integrally involved in development of vaccine candidates and clinical vaccine and prevention trials. International and domestic trial sites are being developed, including a cadre of trained indigenous or minority personnel to conduct vaccine trials with the direct involvement of the communities at risk.

NIH AIDS Vaccine Research Funding



The development of an AIDS vaccine is a complex research challenge because HIV is unusually well-equipped to elude immune defenses, as exemplified by its ability to persist in almost all instances and eventually overcome the immune system. Many different vaccine approaches are being pursued. Initial studies are leading to more advanced vaccine candidates that may provide protection. NIH has now conducted more than 50 Phase I and 2 Phase II clinical trials of nearly 30 vaccine products, individually or in combination, in human volunteers in collaboration with academic investigators and

company co-sponsorship. Many of the early trials involved recombinant HIV envelope protein, the outer coating of the virus. However, complex vaccine products and products that contain other components of HIV have been included in a large number of these trials in the past few years.

To move forward in large-scale vaccine or prevention studies will require major efforts in communities that may be rarely involved in medical research. Capacity building and infrastructure development may need to be undertaken along with information dissemination and education of staff, potential study participants, and community leaders of the groups that will participate in vaccine research.

Clearly, it will be more difficult to formulate an HIV/AIDS vaccine than was the case for prior vaccines directed against acute viral diseases. The scientific community must be mustered to make a broad and diverse attack upon this daunting challenge. Vaccine research is needed to attempt to unravel a wide variety of questions about the structure of the virus, its immunogenicity, the protective role of different components of the immune response, and the mechanisms of viral escape from immune surveillance. In addition, fundamental work must be performed to develop and refine a number of potentially effective methods for presentation of HIV antigens, including vectors engineered from a wide variety of viruses and naked DNA itself. Building on this knowledge base, it will be important to utilize NHP models to elucidate the mechanisms of protective immunity and to screen a multitude of candidate immunogens for the most promising products for clinical trials in humans.

BEHAVIORAL AND SOCIAL SCIENCE

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Better understand and address through interventions the psychological, social, economic, and cultural dynamics of gender and sexuality that play a role in promoting sexual health or conferring sexual risk related to HIV transmission.**
- **Investigate new and changing patterns, contexts, and kinds of substance use (injection and other forms of drugs and alcohol) and their implications for HIV transmission, with an emphasis on associated sexual risk-taking behaviors.**
- **Understand and address the disparate risks and consequences of HIV infection, as well as access, utilization, and quality of prevention and health care services among individuals and groups differing by socioeconomic status, geographic location, gender, sexual orientation, age, and ethnicity.**
- **Identify and address issues related to the initiation, sustainability, and renewal of HIV/AIDS risk reduction efforts at the individual, dyadic, group, and community levels over time, including changing perceptions and risk behaviors associated with the development of new HIV treatments, services, and prevention technologies.**
- **Conduct and support operational and health services research to better understand and address, through interventions, barriers to, and facilitators of, the implementation of science-based HIV/AIDS interventions at the local community level.**
- **Support research on the social, structural, and environmental factors and contexts that contribute to the co-occurrence of HIV/AIDS, other infectious diseases (e.g., TB, STDs, hepatitis), substance use, mental illness, and homelessness; and support intervention research to address such co-occurring conditions.**
- **Support the development of methods and models for assessing the synergistic effects of HIV preventive interventions in a community or society.**

Studies have demonstrated that behavioral change can successfully prevent or reduce the spread of HIV infection in both domestic and international settings. Prevention programs resulting from such studies have altered sexual and drug-using behaviors and have reduced the risk of transmission in many communities and subgroups. NIH supports research to further our understanding of how to change the behaviors that lead to transmission of

HIV (and other diseases, such as hepatitis, STDs, and TB)—including preventing their initiation—and how to maintain protective behaviors once they are adopted in all populations at risk. NIH also supports research on preventing and mitigating the psychosocial consequences of HIV/AIDS on individuals and communities. Three themes cross-cut, and are implicit in, priority areas in AIDS-related behavioral and social science: addressing ethical considerations in the conduct of research; further developing appropriate research methods; and investigating issues in both domestic and international settings as appropriate.

NIH sponsors research related to the following: developing, implementing, and evaluating behavioral and social interventions to reduce HIV transmission in a range of populations and settings; strengthening our understanding of the determinants, trends, and processes of HIV-related risk behaviors and the consequences of HIV infection; developing and evaluating behavioral strategies for preventing or ameliorating the negative physical, psychological, and social consequences of HIV infection; and improving the research methodologies employed in behavioral and social science research.

A more refined understanding of social and cultural factors that contribute to HIV risk or protection, particularly in minority communities, will have an enormous influence on the successful implementation of a broader range of preventive or therapeutic measures. Drug users and their sex partners are the fastest growing segment of AIDS cases in the United States and in many other countries. High priority is being given to research to understand the phenomenon of addiction itself, as well as the complex interaction of alcohol use, drug use, and poor impulse control, and to develop effective interventions from that knowledge base.

The development of new and more effective drug therapies—in particular combination therapies—for combating HIV infection has raised a host of behavioral questions that have significant implications for HIV prevention and treatment. With combination therapies, the number of drugs and frequency of dosing require strict adherence to regimens that may be difficult for many people to achieve. Lack of complete adherence may result in the development of drug-resistant strains of HIV, which could have devastating implications for our ability to stem transmission and treat HIV-infected individuals. In addition, as HIV-infected individuals experience improved health and a decline in detectable virus in their body as a result of taking the new combination therapies, they may believe that they are less infectious and may lapse into unsafe sexual and drug-using behaviors. This could

have the effect of increasing the further spread of the AIDS epidemic. These issues highlight the importance of research on how best to ensure adherence to both pharmacological and behavioral HIV-related interventions.

MICROBICIDES

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Promote innovative mechanisms of funding to attract additional investigators to undertake multidisciplinary research on microbicides discovery and development.**
- **Foster the development of varieties of endogenous and exogenous microbicidal products that are based on specific biological and physiological pathways involving mucosal routes of HIV transmission.**
- **Identify relevant practical and accessible methodologies to assess preclinical/clinical safety and activity of microbicides in a standardized fashion.**
- **Foster the development of combination approaches in acceptable formulations to prevent transmission and acquisition of HIV and other sexually transmitted infections (STIs), such as chemical and physical barriers, and microbicides with different specificities and mechanisms of action.**
- **Promote innovative methods to develop and assess acceptable formulations and modes of delivery for microbicides, bridging knowledge and applications from multiple scientific disciplines.**
- **Expand capacity (infrastructure and human resources) and strengthen coordination to conduct Phase II/III microbicides clinical trials.**
- **Conduct social and behavioral research in concert with microbicides clinical trials, including research on product use, sexual behaviors, and the identification of reliable and valid behavioral measures for use in trials.**

The vulnerability of women to acquiring HIV infection demands the development of effective and acceptable female-controlled chemical and physical barrier methods, such as topical microbicides, to reduce HIV transmission. To enhance and stimulate research in this area, OAR co-sponsored, in 2000, the first international conference devoted to all aspects of microbicide research and development. The conference included more than 600 participants from 45 nations. OAR also provided support for the second international conference in 2002.

NIH is supporting Phase I, Phase II, and Phase III clinical trials of various topical microbicides, as well as behavioral and social research on the

acceptability and use of microbicides among different populations. Beginning in FY 2003, the annual NIH Plan for HIV-Related Research includes a specific research agenda to accelerate microbicide research and to ensure a comprehensive program for screening, discovery, development, preclinical testing, and clinical evaluation of potential spermicidal and nonspermicidal topical agents and other barrier methods.

HIV PREVENTION RESEARCH

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Examine the ways in which social, economic, cultural, and environmental conditions, especially stigma and discrimination, contribute to, or create sources of, HIV-related risk; and develop interventions based on this understanding.**
- **Elucidate the effects of HIV/AIDS treatment availability, delivery, success, and failure—including associated drug adherence and drug resistance—on HIV transmission and acquisition.**
- **Support research on methodologies for developing, implementing, and assessing multidisciplinary, multilevel, multimethod, and cross-cultural HIV preventive interventions.**
- **Investigate and address the psychological, social, and other variables that contribute to the maintenance or erosion over time of protective attitudes, beliefs, and behaviors previously achieved through HIV prevention efforts.**
- **Further explore, develop, and evaluate alternative methods to the randomized controlled trial (RCT) for testing the efficacy of HIV preventive interventions when RCTs are inappropriate or impossible to conduct; and develop guidelines to inform the field about when such (non-RCT) methods are appropriate to employ.**
- **In collaboration with other governmental and nongovernmental organizations, enhance support for operations research and health services research on the design, adaptation, testing, and evaluation of evidence-based strategies to deliver HIV prevention services.**

NIH supports a comprehensive approach to HIV prevention science research that includes contributions from the biomedical, behavioral, and social sciences. The NIH prevention science research agenda targets interventions for both infected and uninfected at-risk individuals to reduce HIV transmission. Our biomedical prevention research priorities include the development of topical microbicides, strategies to prevent MTCT (including a better understanding of risk associated with breast-feeding), management of STDs, and strategies focused on prevention of co-infections, such as HCV in IDUs. NIH also supports behavioral research strategies, including prevention interventions related to drug and alcohol use and risky sexual behaviors. Efforts continue to identify the most appropriate intervention strategies for different populations and subepidemics in the United States and around the world.

NIH's HIV prevention research activities include both basic and intervention studies. Research that elucidates the fundamental mechanisms of human behavior and disease transmission and progression provides the essential basic knowledge needed for the development of testable interventions. Such studies include those that examine the range and interaction of biological, neurological, psychological, familial, social network, and other environmental factors that have an impact on HIV transmission, acquisition, or protection.

RACIAL AND ETHNIC MINORITIES

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Increase the number of NIH-funded minority investigators in HIV/AIDS research to expand their critical mass.**
- **Increase the capacity for multidisciplinary HIV/AIDS research in minority institutions and minority communities through a *sustained* and developmentally staged program.**
- **Increase funded research on the causes of health disparities in HIV/AIDS and effective interventions to reduce these disparities.**
- **Include racial and ethnic minorities in prevention, therapeutic, and vaccine clinical trials in numbers that reflect the current epidemic trends and that address the research questions relevant to racial and ethnic minorities.**
- **Develop, pilot, and evaluate effective interventions to prevent and reduce HIV transmission and its co-morbidities, as well as HIV-related health disparities in racial and ethnic minorities.**
- **Increase information dissemination and technology transfer to racial and ethnic minority communities and community-based organizations, with the explicit goal of increasing their capacity to utilize HIV-related research in meeting their specific needs.**
- **Study those approaches to treatment and adherence that impact health outcomes in racial and ethnic minority communities.**

Research to address the disproportionate impact of the HIV/AIDS epidemic on racial and ethnic minority communities in the United States continues to be a high priority. OAR is directing increased resources toward new interventions that will have the greatest impact on these groups. These include interventions that address the co-occurrence of other STDs, HBV and HCV infections, drug abuse, and mental illness; and interventions that consider the role of culture, family, and other social factors in the transmission and prevention of these disorders in minority communities. NIH is making significant investments to improve research infrastructure and training opportunities for minority researchers and will continue to ensure the participation of minorities in AIDS clinical trials as well as in natural history, epidemiologic, and prevention studies. OAR has provided additional funds to projects aimed at increasing the number of minority investigators conducting behavioral and clinical research; targeting the links between substance abuse, sexual behaviors, and HIV infection; increasing outreach education programs targeting minority physicians and at-risk

populations; and expanding our portfolio of population-based research. One of these projects is a series of Training and Career Development Workshops for racial and ethnic minority investigators. These workshops provide minority investigators with an opportunity to learn about available NIH funding mechanisms and to meet and network with senior minority investigators who receive significant levels of NIH funding.

NIH supports a broad array of behavioral intervention studies with specific focus on African American populations. These studies are characterizing the disease process in drug users, factors influencing disease progression, consequences of multiple co-infections, effectiveness of therapeutic regimens, and impact of health care access and adherence to therapeutic regimens on disease outcomes. The increasing number of minority AIDS cases underscores the importance of behavioral research that continues to define and utilize cultural, social, and contextual factors that affect HIV risk behaviors. The role of alcohol and drug use in facilitating HIV transmission through social networks in all communities also must be explored within these social frameworks.

WOMEN AND GIRLS

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Study the biology of the reproductive tract of HIV-infected and uninfected women and girls, integrating studies of physiology, immunology, and anatomy.**
- **Elucidate a range of host-virus interactions through the course of HIV infection (in particular, during primary HIV infection) and across the life cycle in women and girls.**
- **Develop and conduct clinical studies including biological, therapeutic, vaccine, natural history, epidemiological, behavioral, and social to ascertain the effects of sex and gender in HIV infection among women and girls.**
- **Enhance basic behavioral and social research (theoretical and methodological) on gender construction, maintenance, dynamics, and consequences; and integrate this work into the design and evaluation of HIV prevention and care interventions.**
- **Conduct research on stigma and discrimination associated both with being female and with HIV/AIDS; and integrate this work into interventions to reduce such stigma and its consequences for HIV prevention and care.**
- **Explore factors that influence adoption, use, and effectiveness of women-controlled methods (including physical and chemical barrier methods), alone or in combination, for preventing HIV transmission and acquisition.**
- **Support research to identify effective strategies to improve dissemination and uptake of information from HIV/AIDS research to women and girls and to individuals, communities, and organizations that represent them and/or provide services to them.**
- **Enhance opportunities and mechanisms for recruiting and training biomedical, behavioral, and social scientists in the conduct of interdisciplinary sex and gender analyses in HIV/AIDS research.**

UNAIDS/WHO statistics show that worldwide, there are now almost equal numbers of men and women infected with HIV. According to UNAIDS figures, over 80 percent of all adult infections have resulted from heterosexual sex. Of new infections among women in the United States, CDC estimates that approximately 75 percent of women were infected through heterosexual sex; 25 percent were infected through injecting drug

use. The impact of HIV/AIDS on women and girls is manifested within biological, psychological, and social contexts. To respond to this increasing impact, NIH supports a comprehensive research program—from basic biology to health services research.

NIH-supported basic and clinical research has demonstrated that there are differences in the way HIV infection is transmitted and in its clinical manifestations in women and men. For example, differences have been shown in host-virus interactions, including viral dynamics and the likelihood of being infected with multiple variants. Other NIH studies have demonstrated differences between HIV-infected men and women in metabolic abnormalities and body composition changes. In contrast to men, HIV-infected women exhibit a disproportionate decrease in body fat relative to lean body mass at both early and advanced stages of wasting, a manifestation associated with progression to AIDS. In addition, due to the unique structure and function of the female reproductive tract, women experience gynecological manifestations of HIV infection that have no counterpart in men, giving rise to another critical area of research.

These and other studies have important implications for understanding mechanisms of HIV transmission and pathogenesis in women and for their care and treatment. NIH research is focused on better understanding the differences in clinical manifestations of HIV in men and women and on developing biomedical prevention and treatment strategies that address the needs of women. As part of this effort, NIH continues to place a high priority on the enrollment of women in clinical trials and cohort studies. The Women's Interagency HIV Study (WIHS) and the Women and Infants Transmission Study (WITS) are examples of cohort studies that provide information on the nature and rate of HIV disease progression in women, characterization of clinical manifestations, and the effects of therapeutic regimens.

To better understand the full context of HIV infection in women and girls, NIH supports a multifaceted program of research aimed at (1) understanding the determinants of HIV risk behaviors and the social and cultural contexts that produce vulnerability among women and girls and (2) designing effective interventions to change such behaviors and contexts. Increasing attention is focused on gender dynamics in risk and transmission and how empowering women and girls may enhance protective behaviors. Researchers also continue to explore acceptability and use of female-controlled HIV prevention methods, such as microbicides.

INTERNATIONAL RESEARCH

RESEARCH PRIORITIES OF THE FY 2004 PLAN

- **Develop in-country research and training infrastructure for the conduct of effective prevention and treatment interventions research, integrating new activities into existing health care and prevention services where possible.**
- **Facilitate the rapid initiation of studies of the rational use and feasibility of ART in resource-diverse settings.**

  Define the spectrum of HIV-related illness in diverse geographic settings and develop effective prevention and treatment interventions to limit its impact.
- **Support studies to develop prevention interventions, addressing drug and alcohol use and their associated risks in transmitting and acquiring HIV infection.**
- **Study the interrelationships between stigma and health behaviors such as seeking and/or utilizing prevention and treatment interventions and devise strategies to improve access to and uptake of interventions.**
- **Develop capacity and support for operational and health services research to facilitate the translation of research findings to clinical practice and public health programs in resource-diverse settings.**
- **Address ethical, legal, and human rights challenges in research and implementation of research findings in resource-diverse settings.**

To address the increasing urgency of the global AIDS pandemic, OAR has established a new initiative and strategic plan for global research on HIV/AIDS aimed at slowing the disaster and reversing its destruction of communities, economies, and nations worldwide. The Global AIDS Research Initiative and Strategic Plan reaffirms NIH's long-standing commitment to international AIDS research and will significantly increase research efforts in the coming year to benefit resource- and infrastructure-poor nations. NIH supports a growing portfolio of research conducted in collaboration with investigators in developing countries. Results of this research benefit the people in the country where the research is conducted and people affected by HIV/AIDS worldwide. NIH collaborates with UNAIDS, host country governments, and in-country scientists in development of vaccines and other interventions, in preparation for intervention trials, and in gaining a better understanding of the nature of

the epidemic in diverse geographic settings. NIH-sponsored programs target studies on factors related to HIV transmission and the pathogenic mechanisms associated with HIV disease progression through studies in Africa, Asia, and Latin America. It is critical to the success of international studies that foreign scientists be full and equal partners in the design and conduct of collaborative studies and that they have full responsibility for the conduct of studies in-country. To that end, NIH supports international training programs and initiatives that help to build infrastructure and laboratory capacity in developing countries where the research is conducted.

Training, Infrastructure, and Capacity Building

NIH will continue to support training of domestic and international biomedical and behavioral AIDS researchers as well as the improvement of facilities and equipment for the conduct of AIDS research, including support of animal model research facilities. Numerous NIH-funded programs have increased the number of training positions for AIDS-related research, including programs specifically designed to recruit individuals from minority communities into research careers and to build research infrastructure in minority institutions. The NIH Loan Repayment Program (LRP) was mandated by Congress under Public Law 100-607 in 1988 and authorized under 42 USC 288-1 to encourage health professionals to engage in AIDS-related research at NIH. The AIDS International Training and Research Program (AITRP) was established in 1988 at the request of Congress to train scientists in developing countries to undertake AIDS research. The goal of the program is to expand scientific capabilities in the epidemiology, prevention, diagnosis, and treatment of HIV/AIDS throughout the world and to facilitate the evaluation internationally of AIDS interventions, such as vaccines and other strategies. The Regional Primate Research Centers (RPRC) Program provides specialized facilities, scientific and technical personnel, animal models research and breeding, and a wide variety of NHP species to support diverse requirements for AIDS-related research.

Information Dissemination

Effective information dissemination approaches will continue to be integral to HIV prevention and treatment efforts. Such programs are critical in light of the continuing advent of new and complex antiretroviral treatment regimens, the adherence issues related to HIV/AIDS treatment, the need for research communities to work and communicate globally, and the need to translate behavioral and social prevention approaches into practice. The changing pandemic and the increasing number of HIV infections in specific population groups, such as minorities and women, also underscore the

need to disseminate HIV research findings and other related information to communities at risk. The flow of information among researchers, health care providers, and the affected communities represents new opportunities to rapidly translate research into practice and to shape future research directions.

AIDS Research Benefits Other Research

AIDS research is unraveling the mysteries surrounding many other infectious, malignant, neurologic, autoimmune, and metabolic diseases. AIDS research has provided an entirely new paradigm for drug design, development, and clinical trials to treat viral infections. For example, the drug known as 3TC, developed to treat AIDS, is now the most effective therapy for chronic hepatitis B infection. Drugs developed to prevent and treat AIDS-associated OIs also provide benefit to patients undergoing cancer chemotherapy or receiving anti-transplant-rejection therapy. AIDS research also is providing a new understanding of the relationship between viruses and cancer.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities
NIBIB	National Institute of Biomedical Imaging and Bioengineering

APPENDIX B:

Summary of HIV/AIDS Funding

HIV/AIDS FUNDING BY NIH INSTITUTE, CENTER, AND OFFICE

Institute/Center	FY 2001 Actual	FY 2002 Estimate	FY 2003 Estimate
NIAID	$1,063,074	$1,191,919	$1,350,452
NCI	239,066	256,319	266,539
NIDA	245,397	279,676	304,187
NIMH	145,112	163,938	176,207
NCRR	117,485	135,195	147,198
NICHD	101,851	116,101	126,249
NHLBI	67,437	72,146	75,380
OD	48,494	53,786	58,322
NIGMS	43,298	48,391	52,385
NINDS	37,774	42,366	45,682
NIDDK	24,685	27,642	29,847
NIAAA	21,222	23,979	25,913
NIDCR	21,942	23,473	25,338
FIC	16,149	18,328	21,523
NEI	11,555	12,730	12,777
NIEHS	7,855	8,336	8,682
NINR	9,678	10,990	11,891
NIAMS	5,692	6,467	6,687
NLM	5,589	6,742	7,248
NHGRI	5,809	6,310	6,812
NIA	4,386	4,985	5,379
NIDCD	1,592	1,737	1,738
NCCAM	1,030	2,555	2,718
NIBIB	843	843	843
TOTAL	$2,247,015	$2,514,954	$2,769,997

APPENDIX C:

Office of AIDS Research Advisory Council

OFFICE OF AIDS RESEARCH ADVISORY COUNCIL

Chairperson

Constance A. Benson, M.D.
Vice Chair
Adult ACTG Executive Committee
Professor of Medicine
Division of Infectious Diseases
University of Colorado Health Sciences Center

Executive Secretary

Jack Whitescarver, Ph.D.
Director
Office of AIDS Research
Office of the Director, NIH

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Division of Substance Dependency
University of Colorado Health Sciences Center
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Women's Medical Director
Women and Children Care Center
Columbia University College of Physicians and Surgeons
Columbia Presbyterian Medical Center

Mr. Gregg Gonsalves
Director of Treatment and Prevention Advocacy
Gay Men's Health Crisis

Lawrence O. Gostin, L.L.D., J.D.
Professor of Law
Co-Director
Program on Law and Public Health
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Ashley T. Haase, M.D.
Regents' Professor and Head
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Nancy L. Haigwood, Ph.D
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National Minority AIDS Council

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Former CEO and President
Ingenix Pharmaceutical Services

C. Randal Mills, Ph.D.
Director
Regulatory and Technical Affairs
Regeneration Technologies, Inc.

Julie Overbaugh, Ph.D.
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Fred Hutchinson Cancer Research Center

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John J. Sparkman Center for International Public Health Education
Director
Division of Geographic Medicine
University of Alabama at Birmingham

Mr. Steven F. Wakefield
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Community Education
HIV Vaccine Trials Network

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Professor of Medicine
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Catherine M. Wilfert, M.D.
Professor Emerita Pediatrics
Duke University Medical Center
Scientific Director
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National Advisory Allergy and Infectious Disease Council
Marie Saint-Cyr, M.S.W.
Chair
Board of National Minority AIDS Council
Executive Director
Iris House Center for Women

National Cancer Advisory Board
Elmer Huerta, M.D., M.P.H.
Director
Cancer Preventorium
Washington Cancer Institute
Washington Hospital Center

National Advisory Council on Drug Abuse
Gerald H. Friedland, M.D.
Director
AIDS Program
Professor of Medicine, Epidemiology, and Public Health
Yale University School of Medicine

National Advisory Mental Health Council
Susan Folkman, Ph.D.
Professor of Medicine
Director
Osher Center for Integrative Medicine
University of California, San Francisco

APPENDIX D:

FY 2004 Plan and Budget Timeline

OAR ANNUAL PLAN AND BUDGET PROCESS
FY 2004 Timeline

PLAN	
February 2002	Draft 1 — External Consultants NIH Program Staff IC AIDS Coordinators IC Directors
March 2002	Draft 2 — OAR Advisory Council Comments
July 2002	Final Plan Published
BUDGET	
May 2002	ICs Prepare Budget Using Draft Plan
June 2002	Draft Budget Developed Based on IC Request
August 2002	AIDS Budget Submitted to Director, NIH
August-December 2002	NIH Budget to Secretary, DHHS DHHS Budget to OMB
February 2003	FY 2004 President's Budget to Congress
March 2003	Appropriations Subcommittee Hearings
April-September 2003	House, Senate, Conference Action
October 2003	FY 2004 Begins

APPENDIX E:

List of Acronyms

LIST OF ACRONYMS

ART	antiretroviral therapy
ARV	antiretroviral
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ATI	Analytic Treatment Interruption
ATIS	HIV/AIDS Treatment Information Service
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CFAR	Center for AIDS Research
CIPRA	Comprehensive International Programs for Research on AIDS
CMS	Centers for Medicare and Medicaid Services
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
ddI	dideoxyinosine
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
FIRCA	Fogarty International Research Collaboration Award, FIC
GBV-C	GB virus (hepatitis G)

GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria
GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HERS	HIV Epidemiology Research Study
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trial Network
HPV	human papillomavirus
HRSA	Health Resources and Services Administration
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission

N9	nonoxynol
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization
NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NMAC	National Minority AIDS Council
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
OPHS	Office of Public Health and Science
PBMC	peripheral blood mononuclear cell
PCP	*pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCMI	Research Center in Minority Institution
RCT	randomized clinical trial
RFIP	Research Facilities Infrastructure Program
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SAMHSA	Substance Abuse and Mental Health Services Administration
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis

Th	T helper cells
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VEE	Venezuelan equine encephalitis virus
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infants Transmission Study
WRAIR	Walter Reed Army Institute for Research